REMARKS

Applicant has amended claim 1 to claim a preferred embodiment, wherein the method for diagnosis is performed on a specimen *in vitro*. This amendment is supported throughout the specification, see e.g. pages 9 – 10. Claim 13 is supported at page 10 and claim 14 is supported at pages 16 – 17. Claims 3 and 4 have editorial amendments that do not change what is being claimed and are supported at page 8, lines 28 – 35, and page 2, lines 31 – 35, respectively. As such these amendments do not constitute new matter and their entry is respectfully requested.

The Examiner has objected to the declaration as originally filed because it contained an alteration which was not initialed and dated. Applicant is submitting herewith a new, executed declaration. Accordingly, applicant respectfully submits that this objection should be withdrawn.

Applicant notes that "added page 1" of the Application transmittal paper requested entry of an amendment specifying the proper 35 U.S.C. § 120 statement, but was apparently overlooked. However, to expedite prosecution, applicant is repeating the amendment of the specification to comply with the provisions of 35 U.S.C. § 120. As such, this amendment does not introduce new matter and its entry is respectfully requested.

The Examiner objected to the use of the trademarked term "Puregene." Applicant respectfully submits that the amendment to the specification has obviated this objection, and respectfully requests that it be withdrawn.

Claims 1 – 4 were rejected under 35 U.S.C. § 112, first paragraph.

Applicant respectfully submits that this rejection should be withdrawn for the following reasons.

Applicant appreciates the Examiner's indication that the specification enables a method for diagnosing melanoma which comprises contacting a biological specimen of malignant cells

in vitro with a probe that selectively recognizes microphthalmia (Mi), wherein the biological specimen does not include melanocytes, mast cells or osteoclasts.

In order to expedite prosecution, applicant has now amended the claims to indicate that the method of diagnosis is performed on a biological specimen *in vitro*, without prejudice to filing an application also directed to the *in vivo* use.

The Examiner has also contended that the use of Mi as a useful diagnostic marker is limited by its expression in normal melanocytes, osteoclasts, and mast cells. Specifically, the Office alleged that if one looked at a specimen that contained a mixed population of cell types, including osteoclasts, it would be impossible to distinguish melanoma cells expressing Mi from healthy osteoclasts which also express Mi.

Applicant respectfully disagrees for several reasons. As will be explained in more detail, it is very easy to distinguish between normal (non-malignant) and malignant cells. Claim 1 specifies that it is not just the presence of Mi, in the sample that is indicative of melanoma, but further requires its expression in malignant cells. More specifically, Mi is useful for distinguishing melanoma from other possible cancers, not for distinguishing cancerous cells from healthy cells (such as normal melanocytes). That distinction, between malignant and non-malignant cells, is possible without any special stains, because it is trivial to discriminate between melanoma cells and healthy cells such as melanocytes, osteoclasts, and mast cells, based on the characteristic morphology of cancer cells. For example, neoplastic cells do not exhibit normal cell contact inhibition and thus will grow on top of each other, piling up and/or growing as a mass. These differences can be seen for example in Figure 6. Healthy cells, however, including normal melanocytes, osteoclasts, and mast cells, are thus readily distinguished from such transformed cells simply by their morphology. Any staining of healthy cells by Mi will not be recognized by the

skilled artisan as a false positive. Thus, the Mi marker is not required to discriminate healthy cells from cancerous cells, but to diagnose the type of cancer cells present in a specimen. As explained at page 2 of the specification, determining the origin of a metastatic tissue arising from a melanoma is extremely difficult. A skin melanoma can be removed, yet come back later at a different site, or a different metastatic disease can arise years later at the same site a melanoma was removed from. However, the implications for treatment can be very different depending upon the particular cancer one is looking at. Thus, the present method is interested in identifying a malignant cell as being a melanoma.

Furthermore, in looking at a biological specimen for diagnosing melanoma, any melanocytes, osteoclasts, or mast cells incidentally present would not confound diagnosis. Osteoclasts reside in the bone and thus are extremely unlikely to even be present in such a specimen. Similarly, mast cells and melanocytes are also not likely to be present in most samples. Melanocytes are a rare cell type in human skin. When looking at a skin lesion for diagnosing melanoma, some normal cells are typically included at the margins of the tumor. Thus, any melanocyte incidentally present in such a specimen would be found in the border zone surrounding the tumor, not in the actual cancer itself. Moreover, in any non-skin specimen being tested, normal melanocytes would not be present because normal melanocytes do not invade beyond the skin. This also eliminates the danger of false positives.

The Examiner has also indicated that the use of Mi as a diagnostic marker for melanoma is confounded by the existence of three isoforms. It was contended that MITF-M is expressed in melanocytes and melanoma cells, whereas MITF-A is expressed in many cell types and MITF-H is expressed in heart cells. However, for all of the reasons described above, the ability of an Mi probe to discriminate between these isoforms will not effect its utility for diagnosing melanoma.

What is important for the present method is the positive staining of tumor tissue with an Mi probe. The presence of such Mi in the malignant cell indicates a positive diagnosis of melanoma, just as was taught and claimed in the application. Moreover, the broad teaching of the specification, which indicated that expression of Mi in cancer cells is diagnostic of melanoma, has been repeatedly confirmed in practice.

Accordingly, applicant respectfully submits that all claims comply with 35 U.S.C. § 112, first paragraph.

Claims 1 – 4 were also rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicant has amended the claims to expedite prosecution. Applicant respectfully submits that the amendments to the claims have obviated this rejection.

Accordingly, applicant respectfully submits that all claims comply with 35 U.S.C. § 112, second paragraph.

Applicant respectfully submits that all claims are in condition for allowance. Early and favorable action is requested.

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